acid position 182 as disclosed in Figure 2 of applicants' originally filed patent application. Figure 2 shows the stop codon "TAA" starting at nucleotide position 647 of plasmin-like polypeptide (PLP) gene. SEQ ID NO:4 of the previously filed Sequence Listing inadvertently listed an erroneous protein extending through this stop codon. Support for this amendment is found in originally-filed Figure 2. No new matter has been added.

Pending Claims 11-16 of the above-identified patent application stand finally rejected by the Examiner, because (i) the claimed invention allegedly is neither supported by a well-established utility, nor a credible, specific and substantial *utility* at the time of filing (35 U.S.C. § 101), and (ii) because one skilled in the art allegedly would not know how to use the claimed invention in view of the asserted lack of utility (35 U.S.C. § 112 ¶1).

A NOTICE OF APPEAL, dated 02 May 2002, was timely filed. The claims, as originally filed, have not been amended.

Applicants maintain their respectful traverse of these rejections and incorporate and reaffirm herein applicants' arguments and proofs of record.

Applicants thank the Examiner for the opportunity to further discuss the *utility* of applicants' subject matter in the recent Examiner's Interview of October 17, 2002, wherein the Examiner encouraged applicants' patent counsel to further clarify the structure/function arguments relating to the subject human plasmolipin polypeptide, by submission of additional supporting documents.

Applicants respectfully request reconsideration of present application, entry of the present Response, withdrawal of the Examiner's 35 U.S.C. §§ 101 and 112 ¶1 rejections, and allowance of all pending claims in view of the following arguments and the attached APPENDICES, all of which provide compelling support for not only a well-established utility, but also a credible, specific and substantial *utility* for the subject polypeptide and coding sequence as of the time of filing.

Rejection under 35 U.S.C. § 101

The Examiner rejected claims 11-16, under 35 U.S.C. § 101, as being neither supported by a well-established utility, nor a credible, specific and substantial *utility* at the time of filing. In essence the Examiner's position of record on the lack of *utility* of applicants' human plasmolipin polypeptide is that high homology (*i.e.*, sequence identity) between or among two or more

polypeptides is insufficient ***per se*** to establish either a well-established utility, or a credible, specific and substantial *utility* (*see* final Office Action of 02 November 2001, *citing* particular literature articles and proffering PTH and PTHrP as specific examples).

Applicants thank the Examiner for the thoughtful discussion of the references cited in the Office Action of 02 November 2001, and appreciate the Examiner's articulated position. However, even if applicants agreed (which they do not) with the Examiner's narrow characterization of the art with respect to the general probative value of sequence identity in establishing function, applicants do not rest their assertion of utility *solely* on sequence identity. Rather applicants contend that utility is additionally supported by (𝔸) ***overwhelming and substantial structural homology***, (𝔹) the fact that in particular protein families, such as the present one, there are characteristic structural/functional features that, even in the absence of substantial overall sequence identity, are recognized in the art as ***functional hallmarks***, and (ℂ) applicants' polypeptide is, as disclosed at the time of filing, in fact recognized and referred to in the art as ***the*** human plasmolipin.

(𝔸) It was appreciated at the time of filing that there are overwhelming and substantial structural homology between applicants' human plasmolipin polypeptide and rat plasmolipin (regarded in the art to function, *inter alia*, as an ion channel). This overwhelming and substantial structural homology is summarized in detail in the Affidavit of David Duhl (AFFIDAVIT), attached hereto as APPENDIX A (*see*, in particular paragraph 8 and TABLE I thereof). Significantly, the underlying premise of applicants' characterization of the structural homologies summarized in TABLE I of the AFFIDAVIT follows directly from art at the time of filing; namely, Fischer & Sapirstein *J. Bio. Chem.* 269:24912-19, 1994, and Gillen et al., E. J. Neuroscience 8:405-414, 1996 (and references cited therein), both attached as EXHIBIT 2 of the AFFIDAVIT (*see*, in particular, Figure 5 of Fischer & Sapirstein, at page 24916, and as discussed in the bridging paragraph from page 24915; *and see also* Figure 8 of Gillen et al., at page 412).

Based on this analysis, applicants contend that it is *unquestionable* that at the time of filing, applicants' subject polypeptide would have been regarded as human plasmolipin by those of ordinary skill in the relevant art, and would have been regarded as having analogous functions, based on the fact that it is expressed (applicants' Northern blots) in relevant human tissues.

(𝔹) Applicants respectfully contend that the Examiner's analysis of record, while relevant and informative, fails to appropriately acknowledge that there are some protein families that

comprise structural/sequence hallmarks recognized in the relevant art as defining function for that particular family, even in the absence of substantial overall sequence identity. Significantly, applicants' subject polypeptide not only has high sequence identify and structural homology, but also comprises such a defining structural/sequence hallmark.

Specifically, applicants' subject polypeptide contains the following sequence that is located at the junction of the first extracellular loop and the second transmembrane domain:

-[Q/Y-G-W-V-M-F/Y-V-S/A-V/L]-

See AFFIDAVIT at TABLE I, last row of data.

This hallmark structure, as discussed by Magyar, et al., Gene 189:26-275, 1997, uniquely identifies (as of the time of filing) a subgroup of tetraspan proteins which are associated with myelin (*Id*, see in particular Figure 2, A and B). This subgroup comprised, *inter alia,* at the time of filing, MAL, rat plasmolipin, and BENE (*Id*). As described by Magyar et al., this amino acid motif is exclusively found in members of the MAL protein family. Moreover, Northern blot analysis of MAL shows expression in spleen, kidney, spinal cord, brain, and peripheral nerves, consistent with the expression of applicants' subject sequence (*Id*). Significantly, the extent of sequence identity among the MAL myelin associated polypeptide family ranges from 25 to 91 percent, with the extent of sequence identity between rat plasmolipin and rat MAL being only 27%. Thus, in combination with the above defining motif, even a 27% sequence identity is sufficient to place a novel protein in the MAL subfamily of tetraspan proteins.

Applicants contend that one of ordinary skill in the art would, unquestionably, have identified applicants' subject polypeptide as a functional member of the MAL, plasmolipin, BENE, etc. subfamily of myelin-associated polypeptides, based not only on the gene expression profile and extent of sequence identity, but also on the substantial and overwhelming structural homology, and in particular based on the presence of the defining hallmark -[Q/Y-G-W-V-M-F/Y-V-S/A-V/L]- motif.

(C) Applicants' subject polypeptide sequence is not only recognized in the art as a plasmolipin-like polypeptide, but is in fact also widely recognized as ***the*** human plasmolipin. Specifically, two significant conclusions can be drawn by analysis of representative current tetraspan/plasmolipin literature.

First, the structure/function analysis of Fischer & Sapirstein, *supra*, and of Gillen et al., *supra*, was not only widely known in the art at the time of filing, but also continues to be the art-recognized standard for evaluation of new tetraspan protein sequences (*e.g.*, Magyar et al., *Gene* 189:269-275, 1997, attached here to as APPENDIX B; Hamacher et al., *Mammalian Genome* 12:933-937, 2001, attached here to as APPENDIX C). For example, the Fischer & Sapirstein model was used to identify a cloned mouse cDNA sequence as mouse MAL (Magyar et al, *supra*).

Therefore, applicants' continued reliance thereon for the purposes of the instant Response, is appropriate and fully validated by the art, and there is no question that applicants' conclusions regarding structure and function of the subject polypeptide are representative of one skilled in the relevant art at the time of filing of the present patent application.

Second, applicants' subject polypeptide sequence ***is in fact recognized in the art as the human plasmolipin***—a conclusion fully disclosed, taught and enabled in applicants' originally filed patent application.

For example, in Hamacher et al., *supra*, a rat plasmolipin cDNA was used to clone the mouse plasmolipin gene. In the analysis of the mouse gene, Hamacher et al performed an alignment search against rat (Gillen et al., 1996, EMBL Z49858) and human (Xie et al. unpublished, EMBL AF137386) plasmolipin cDNA, and concluded that "[i]n general, the coding region of plasmolipin is highly conserved throughout the mammalian species rat, mouse and human, as shown here, with an average homology of approximately 90%" (*see* Hamacher et al., at page 935, first paragraph under "Discussion").

Therefore, those of ordinary skill in the relevant art not only continue to use the Fischer & Sapirstein structure/function model to assess new cloned tetraspan genes, but also regard applicants' disclosed polypeptide sequence as *the* human plasmolipin as disclosed, taught and enabled by applicants. There is thus no question that one skilled in the art at the time of filing would regard applicants' human plasmolipin as having not only a credible, specific and substantial *utility*, but also a well-established utility; namely, that of a MAL/plasmolipin family member. Plasmolipins were known in the art at the time of filing to function as voltage-dependent K^+ channels (Fischer et al., *Neurochemical Research* 19:959-966, 1994, attached hereto as APPENDIX C) and were recognized as being involved in, *inter alia*, neurogenesis and various art-recognized demyelization conditions.

Applicants, in view of the attached AFFIDAVIT and above arguments, respectfully request

withdrawal of the Examiner's utility rejection under 35 U.S.C. § 101, because there is not only a well-established utility, but also a credible, specific and substantial utility.

Rejection under 35 U.S.C. § 112

The Examiner also rejected claims 11-16, under 35 U.S.C. § 112 ¶1, because one skilled in the art allegedly would not know how to use the claimed invention in view of the asserted lack of utility (35 U.S.C. § 112 ¶1).

Applicants, in view of the attached AFFIDAVIT and above arguments, respectfully request withdrawal of the Examiner's utility rejection under 35 U.S.C. § 112 ¶1, because one skilled in the art would in fact know how to use the claimed invention in view of applicants' disclosed teachings at the time of filing, said teaching including not only a well-established utility, but also a credible, specific and substantial utility.

Concluding Remarks

Applicants emphatically maintain that requisite utility, as described above and in the record, has been shown. Applicants respectfully contend that the Examiner's homology analysis, while relevant and thoughtful in most respects, has inadvertently misconstrued the art by failing to appropriately recognize that, while function cannot always be determined from sequence homology, function for certain *particular* protein subfamilies can be—where an overwhelming structural homology and defining features exist. Such is the case, as described herein above, for the MAL gene family, and the instant polypeptide. Applicants' disclosure of the subject protein as a MAL/plasmolipin subfamily member amounts to an adequate assertion of utility, because of the special characteristics of this protein subfamily, as defined herein.

Specifically, applicants do *not* base their *utility* position on sequence homology (*i.e.*, identity) *per se*. Rather, utility is based on the combined facts that applicants' human plasmolipin sequence has **(i)** very high sequence identity, **(ii)** overwhelming/substantial structural homology, **(iii)** comprises a defining sequence motif (-[Q/Y-G-W-V-M-F/Y-V-S/A-V/L]-) that is an art-recognized hallmark of the MAL/plamsolipin subfamily of tetraspan proteins, **(iv)** is expressed via a discrete mRNA species in particular human tissues reflective of the expression of other members of the MAL gene family, and **(v)** is in fact regarded in the art as the human plasmolipin polypeptide—*all as disclosed, taught and enabled in applicants' originally filed patent*

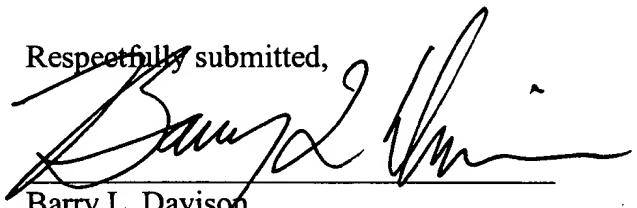
application.

Significantly, the Examiner's *utility* position falls short of that which might be expected under the current utility guidelines if applicants had disclosed an **EST** comprising only a partial plasmolipin open reading frame. Under the current guidelines, even such an EST has requisite utility if it can be used for a *unique* use (other than screening for the corresponding full-length cDNA or genomic clone). For example, even such an EST, as fully disclosed, taught and enabled by the Northern blot analysis and relevant discussions in applicants originally filed patent application, could function as a unique probe for monitoring K^+ ion channel expression during neurogenesis in either human (or rat or mouse; given the high sequence identity).

Applicants have not disclosed a mere EST with a partial open reading frame. Rather applicants have disclosed and characterized the full-length coding sequence and protein which, as originally taught by applicants, is now widely regarded in the art as ***the*** plasmolipin protein. Additionally, applicants have disclosed that this sequence is expressed as a specific mRNA species, that such expression is consistent with that of other MAL subfamily members, and importantly that such sequences (or antibodies to the subject protein) could be used, *inter alia*, to monitor K^+ channel expression during neurogenesis or in demyelization disorders.

Applicants, in view of the above arguments, amendments and the attached AFFIDAVIT, respectfully request reconsideration of the present application, entry of the present Response, withdrawal of the Examiner's rejections under 35 U.S.C. §§ 101 and 112 ¶1, and allowance of all pending claims 11-16.

Respectfully submitted,



Barry L. Davison
Registration No. 47,309
For Jane E. R. Potter
Registration No. 33,332
Attorneys for Applicants

Davis Wright Tremaine
2600 Century Square
1501 Fourth Avenue
Seattle, Washington 98101
Telephone (206) 628-7621
Facsimile (206) 628-7699